REVIEW ARTICLE

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Pleural Disease

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THE PLEURAL SPACE IS DEFINED BY THE VISCERAL PLEURA, WHICH COVERS the lung, and the parietal pleura, which covers the chest wall, diaphragm, and mediastinum. It is estimated that pleural effusion develops in more than 1.5 million patients each year in the United States, with the majority of cases resulting from congestive heart failure, pneumonia, and cancer.[1] Spontaneous pneumothorax affects approximately 20,000 patients annually in the United States, and the incidence of iatrogenic pneumothorax is similar.[1] Over the past several years, substantial advances have been made in our understanding of pleural biology and related pathophysiology, as well as in the treatment of parapneumonic effusions, empyema, and malignant pleural effusions and in our understanding of the high mortality associated with nonmalignant and transudative effusions. In addition, the definitions and management of pneumothorax have also recently evolved. For these conditions, the goals of patient care are expeditious and efficient diagnosis with minimally invasive interventions that avoid the need for multiple procedures, that minimize hospital days, and that maximize quality of life. This review considers these various aspects of pleural disease.

PLEURAL ANATOMY AND PATHOPHYSIOLOGY

When normal lungs are removed from the chest cavity, their gas volume decreases as a result of elastic recoil. The chest wall, in contrast, when opened to atmospheric pressure at the end of a normal breath (i.e., at functional residual capacity), tends to expand. This balance of physical forces keeps the pressure in the pleural space slightly negative, at approximately –3 to –5 cm of water.[2,3] The physiological function of the pleural space in humans is unclear. One theory maintains that the pleura serves as an elastic serous membrane to allow changes in lung shape with respiration, whereas others suggest that the slightly negative pleural pressure at functional residual capacity prevents atelectasis by maintaining positive transpulmonary pressure.[2,4] Elephants, however, do not have a pleural space; they instead have layers of loose and dense connective tissue between the lung and chest wall, and they seem to do just fine. It is postulated that if elephants did have a pleural space, the pressure gradient between the atmosphere and their submerged thorax (approximately 150 mm Hg) when they are "snorkeling" across a river would both rupture the small pleural capillaries and create large transudative pleural effusions.[5,6] In fact, humans fare quite well after obliteration of the pleural space (pleurodesis), with substantial alleviation of dyspnea if a pleural effusion or pneumothorax had been present. In humans, the parietal and visceral pleura merge at the hilum of the lungs, separating the thorax into two noncontiguous spaces (the hemithoraxes). The North American bison, in contrast, has in some cases been found to have an incomplete mediastinum; this makes it possible to kill these large animals with a single arrow or gunshot to the chest, which creates bilateral pneumothoraxes.[7]

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When considering the pleura, it is important not to think only of the pleural space, since both the visceral and parietal pleurae play important roles in maintaining normal homeostasis. The pleurae are covered by mesothelial cells, which are metabolically active and produce many substances, including hyaluronic acid–rich glycoproteins, nitric oxide, and transforming growth factor β.[1] Research over the past several years has greatly enhanced our understanding of pleural liquid formation and resorption.[8,9]

In typical humans, it is estimated that approximately 0.26 ml of fluid per kilogram of body weight is contained within each pleural cavity.[4,10,11] This fluid is both produced and absorbed primarily on the parietal surface[2,12] and is dependent on the balance of hydrostatic and oncotic pressure differences between the systemic and pulmonary circulations and the pleural space (Fig. 1). Lymphatic vessels lying in the parietal pleura are responsible for pleural fluid resorption, and the flow rate of these vessels can increase by a factor of approximately 20 in response to increases in pleural liquid formation.[12] Thus, a clinically significant effusion will be seen only when fluid production substantially overwhelms the ability of the lymphatic vessels to resorb fluid, because of high production, diminished resorption, or a combination of these two factors.

EVALUATION OF PLEURAL EFFUSIONS

The differential diagnosis for pleural effusions is extensive; a list of potential causes is shown in Table 1. A systematic and expeditious evaluation is essential, since a delay in making some diagnoses (e.g., empyema) is associated with increased morbidity and mortality.[13] The use of point-of-care ultrasonography in the evaluation of pleural effusions has been associated with a higher rate of successful aspiration of fluid from the pleural space than when no imaging is used, more accurate quantitation of the volume of effusion than can be obtained with chest radiography, more accurate detection of septations than can be obtained with computed tomography (CT) of the chest, an improvement over radiography in the ability to identify exudative effusions and malignant effusions, and perhaps most important, fewer complications than when ultrasonography is not used to guide pleural procedures.[14-20] Thus, ultrasonography is strongly recommended by the British Thoracic Society to guide pleural intervention.[21,22] Unless the cause of the effusion is relatively straightforward (e.g., in a patient who presents with shortness of breath, paroxysmal nocturnal dyspnea, orthopnea, and lower-extremity edema with elevated jugular venous distention and an effusion that is more pronounced on the right side than on the left, all of which are suggestive of congestive heart failure), a chest physician should be involved to help ensure the timely evaluation of pleural effusion,[21] to decrease the likelihood of associated complications, and to ensure appropriate follow-up based on the results of pleural fluid analysis.[20,23]

TRANSUDATES VERSUS EXUDATES

One of the first steps in the evaluation of patients with pleural fluid is to distinguish those who have inflammatory (exudative) effusions from those who have noninflammatory (transudative) effusions.[24] The use of Light's criteria for differentiating exudative from transudative effusion, initially described in 1972, has remained the standard method over the past 45 years.[25] According to Light's criteria, a patient is considered to have an exudative effusion when any one of the following findings is present: a ratio of pleural fluid protein to serum protein higher than 0.5, a ratio of pleural fluid lactate dehydrogenase (LDH) level to serum LDH level higher than 0.6, or a pleural fluid LDH level higher than 200 IU per liter (or >67% of the upper limit of the normal range for serum LDH level).[25,26]

Although these criteria correctly identify nearly all exudates, approximately 25% of transudates are misclassified as exudates, especially in patients who have underlying congestive heart failure and have received diuretics.[27,28] In patients with suspected congestive heart failure who are receiving diuretic therapy, a serum protein level that is more than 3.1 g per deciliter higher than that in pleural fluid or a serum albumin level that is more than 1.2 g per deciliter higher than that in pleural fluid has been suggested to help identify transudates that were misclassified as exudates with the use of Light's criteria. However, the overall accuracy of that approach has not been found to be significantly higher than that with Light's criteria.[28,29]

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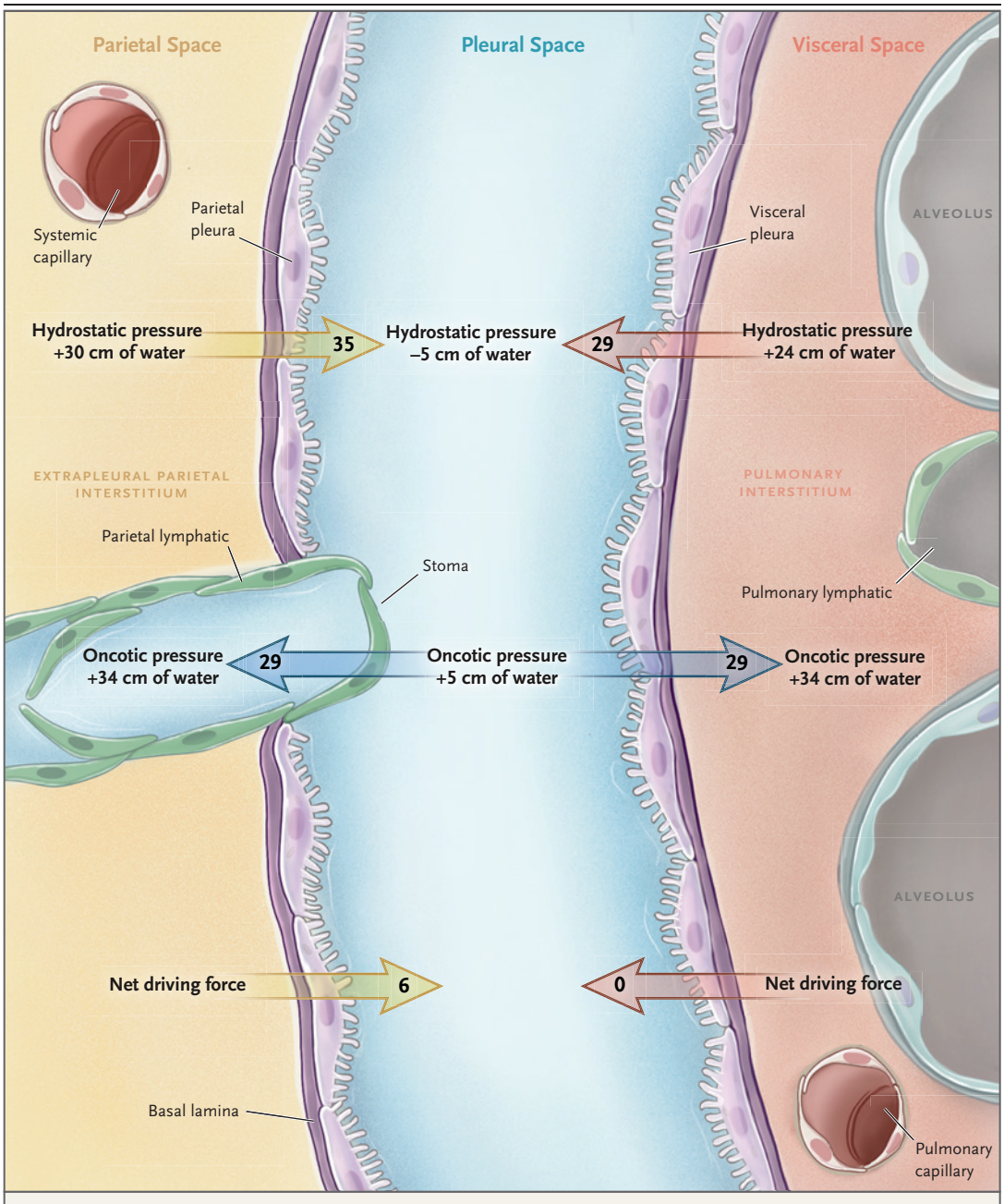

Figure 1. Balance of Forces Regulating Pleural Fluid Formation.

The amount of fluid in the pleural space is dependent on the balance of hydrostatic and oncotic pressures between the parietal and visceral pleura and the pleural space. Because hydrostatic pressures are higher on the parietal pleura than on the visceral pleura and the oncotic pressures are equivalent, pleural fluid is primarily produced from the parietal pleura. Likewise, the lymphatic vessels on the parietal pleura are responsible for the majority of pleural fluid resorption.

Similarly, a pleural fluid level of N-terminal pro–B-type natriuretic peptide (NT-proBNP) higher than 1500 pg per milliliter has been shown to accurately identify effusions due to heart disease such as congestive heart failure; however, since serum levels of NT-proBNP are nearly identical to pleural fluid levels, current recommendations suggest using the serum NT-proBNP level and clinical judgment to correctly identify transudates in patients who have been undergoing active

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diuresis for congestive heart failure in the context of a pleural fluid collection.[30,31] If serum levels of protein and albumin are not available (e.g., in an outpatient who hopes to avoid venipuncture), a pleural fluid protein level higher than 3 g per deciliter or a pleural fluid cholesterol level higher than 45 mg per deciliter has been shown to indicate the presence of an exudative effusion as accurately as Light's criteria.[26,32-34]

COMMON EXUDATES

PARAPNEUMONIC EFFUSIONS AND EMPYEMA

The most common exudative effusions are those associated with an underlying pneumonia, so-called parapneumonic effusions.[1] Empyema refers to frank infection or pus in the pleural space. The clinical significance of empyema and the importance of its drainage have been known for more than 2000 years, and Hippocrates has been quoted as saying, "Persons who become affected with empyema after pleurisy, if they get clear of it in forty days from the breaking of it, escape the disease; but if not, it passes into phthisis."[35,36] Despite advances in the treatment of pneumonia, however, mortality is higher among patients who have an associated parapneumonic effusion than among patients with pneumonia and no effusion,[37,38] and delays in drainage are associated with substantially higher mortality.[13] In addition, both the incidence of and mortality due to parapneumonic effusion and empyema continue to rise.[39,40] Of note, elderly patients often do not present with the classic symptoms of cough, fever, sputum, and chest pain, but rather with anemia, fatigue, and failure to thrive. Probably in part because of underdiagnosis, elderly patients also often have more complicated effusions when they are diagnosed, as well as higher rates of failure of nonsurgical therapy.[41] Thus, it is crucial to consider parapneumonic effusion and empyema in all elderly patients with pneumonia.

A cornerstone of treating parapneumonic effusion and empyema is the selection of appropriate antibiotics on the basis of local microbiology and antibiotic resistance. Patients with community-acquired pneumonia tend to be infected with streptococcus species and anaerobes (e.g., bacteroides and peptostreptococcus), whereas patients with hospital-acquired infection are more likely to have methicillin-resistant staphylococcus and gram-negative bacteria (e.g., enterobacter).[42]

Table 1. Causes of Pleural Effusions.

Transudative effusions
Congestive heart failure
Cirrhosis
Nephrotic syndrome
Glomerulonephritis
Peritoneal dialysis
Hypoalbuminemia (typical serum albumin, <1.5 mg/dl)
Atelectasis
Superior vena cava obstruction
Trapped lung
Sarcoidosis
Myxedema
Cerebrospinal fluid leak or ventriculopleural shunt
Urinothorax
Pulmonary arterial hypertension
Pulmonary embolism
Pericardial disease
Extravascular migration of central venous catheter
Exudative effusions
Infectious: bacterial, viral, tuberculosis-related, fungal, parasitic
Neoplastic: metastatic disease (e.g., lung cancer, breast cancer, lymphoma, myeloma, ovarian cancer, pancreatic cancer, cholangiocarcinoma), mesothelioma, primary body-cavity lymphoma
Paramalignant effusions: reactive pleuritis due to underlying lung cancer, airway obstruction or atelectasis, radiation-induced pleuritis
Reactive: reactive pleuritis due to underlying pneumonia (i.e., parapneumonic)
Embolic disease: pulmonary embolism
Abdominal disease: pancreatitis, cholecystitis, hepatic or splenic abscess, esophageal perforation after esophageal varix sclerotherapy
Cardiac or pericardial injury, including myocardial infarction (after coronary-artery bypass, cardiac surgery, or cardiac ablation procedures), pulmonary-vein stenosis
Gynecologic: ovarian hyperstimulation, Meigs' syndrome, endometriosis, postpartum complications
Collagen vascular disease: rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, familial Mediterranean fever, eosinophilic granulomatosis, granulomatosis with polyangiitis
Medications: nitrofurantoin, dantrolene, methysergide, dasatinib, amiodarone, interleukin-2, procarbazine, methotrexate, clozapine, phenytoin, β-blockers, ergot drugs
Hemothorax
Chylothorax (most commonly seen after trauma or in patients with lymphoma)
Sarcoidosis
Lymphoplasmacytic lymphoma
Cholesterol effusions (commonly seen in tuberculosis, rheumatoid effusions, and any other chronic pleural effusion)
Miscellaneous: benign asbestos pleural effusion, yellow nail syndrome, uremia, drowning, amyloidosis, electrical burns, iatrogenic effusion, capillary leak syndromes, extramedullary hematopoiesis

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Mortality is significantly higher among patients with hospital-acquired infection than among those with community-acquired infection (47% vs. 17%).[42] Rahman and colleagues have developed a scoring system called RAPID (renal function, age, purulence, infection source, and dietary factors) to help identify patients who are at risk for a poor outcome at the time of their presentation.[43] Scores range from 0 to 7, with values between 0 and 2 assigned for renal function and age (with higher scores given for worse renal function or older age) and scores of 0 or 1 assigned for purulence of the effusion (a nonpurulent effusion receives a score of 1), whether the infection was hospital acquired (score of 1) or not (score of 0), and dietary factors (a score of 0 is assigned for an albumin level ≥2.7 g per deciliter and a score of 1 is assigned for a value below that threshold). In one study, patients in the high-risk category (those with a RAPID score of 5 to 7) were found to have at least a 30% chance of dying in the subsequent 12 weeks, and thus similar patients may warrant more invasive initial therapy.

Patients with parapneumonic effusions or empyema have the potential for a deterioration in their condition, and, given their underlying inflammatory state, all such patients should undergo peripheral-blood culture and should receive adequate nutrition and prophylaxis for deep-vein thrombosis.[44] As with any other infection in a closed space, empyema needs to be drained. Although data from randomized trials are lacking, studies of large retrospective series have shown that small-bore tubes (≤14-French) perform on par with larger-bore tubes in terms of subsequent mortality and the need for surgery and are associated with less pain during insertion and while in place.[45] However, since tubes smaller than 12-French have a higher failure rate[46] in empyema, our practice is to use a 14-French pigtail catheter placed with the modified Seldinger technique. If the pleural space is not drained with a small-bore tube, the instillation of tissue plasminogen activator (t-PA) and DNase has been successful and in one trial was found to be associated with significantly better fluid drainage, a lower likelihood of being referred for surgery, and a shorter mean hospital stay.[47] It should be noted, however, that t-PA and DNase have not been shown to decrease mortality, and the cost of six doses of t-PA–DNase is approximately $7,000 (Rowden A, Johns Hopkins Hospital: personal communication). The mean hospital stay among patients in the t-PA–DNase group in that trial was 12 days.[47]

In addition, the avoidance of surgery may not be the most important outcome measure, since video-assisted thoracoscopic surgery (VATS) is far less invasive than thoracotomy. Older, although smaller, randomized trials showed that VATS can be the definitive treatment for empyema in up to 91% of cases,[48] and more recent data on VATS suggest that hospital stays of approximately 5 to 7 days are usual.[49-51] Furthermore, when performed later in the course of the disease, surgery is associated with a higher conversion rate to thoracotomy and more complications than when it is performed earlier in the disease process.[52] Our general approach to patients with parapneumonic effusion or empyema is based on the recommendations from the British Thoracic Society[44] and is shown in Figure 2. There is currently a planned randomized trial evaluating t-PA–DNase versus early VATS for the treatment of parapneumonic effusion or empyema and studies examining whether reduced dosing regimens of t-PA–DNase and even irrigation with normal saline can achieve similar results.[54]

MALIGNANT PLEURAL EFFUSIONS

Malignant pleural effusions are the second leading cause of exudative effusions and the leading cause of exudates among patients who undergo thoracentesis; they account for more than 125,000 hospital admissions per year in the United States, with estimated inpatient mortality of 11.6% and associated hospital charges of more than $5 billion per year.[55] The majority of malignant pleural effusions arise from lung cancer, breast cancer, and lymphoma, and it is estimated that 15% of patients with lung cancer will have a malignant pleural effusion at presentation and up to 50% will have a malignant pleural effusion during the course of their illness. Malignant pleural effusion is associated with a poor prognosis, with a median survival of 4 to 7 months from the time of diagnosis.[56,57] Even among patients whose effusions are considered "too small to tap," survival is significantly shorter than among patients without any effusion.[57] Survival

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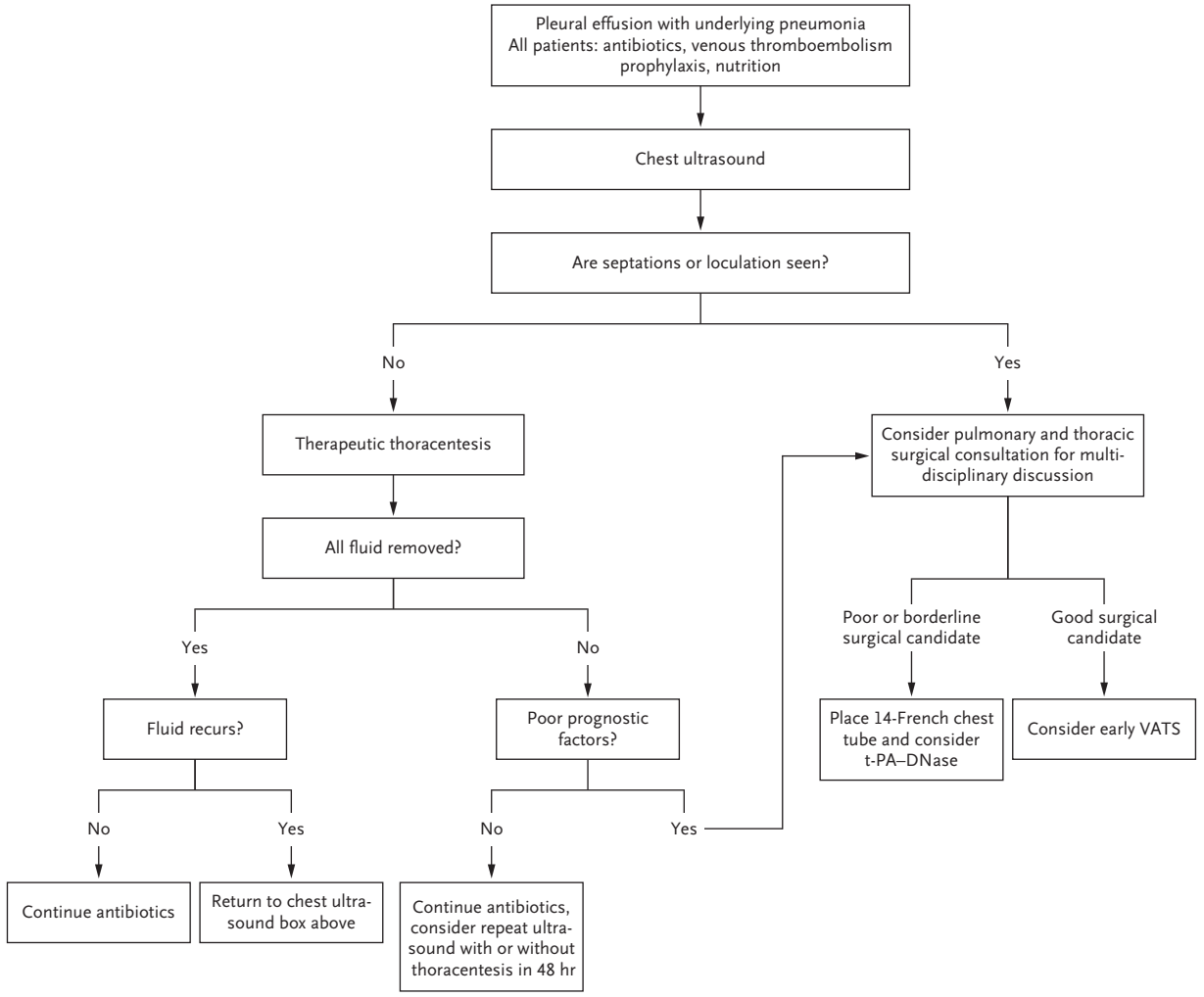

Figure 2. Management of Parapneumonic Effusions.

Poor prognostic factors after incomplete removal of fluid by means of therapeutic thoracentesis include pus in the pleural space, positive Gram's stain or culture, pleural fluid glucose level less than 40 mg per deciliter, pleural fluid pH lower than 7.15, and pleural fluid lactate dehydrogenase level more than 3 times the upper limit of the normal range for serum.[1,53] A decision regarding surgery depends on the patient's clinical status and ability to undergo surgery, as well as on local resources and the availability of a skilled surgeon. The figure is modified from Davies et al.[44] The abbreviation t-PA denotes tissue plasminogen activator, and VATS video-assisted thoracoscopic surgery.

depends primarily on tumor subtype, with lung cancer and gastrointestinal cancers having the worst outcomes (median survival, 2 to 3 months) and mesothelioma and hematologic cancers having the best prognosis, with survival approaching 1 year.[58,59]

To appropriately treat patients with malignant pleural effusions, it is crucial to understand the mechanisms by which pleural effusions cause dyspnea. Although pleural effusions mildly increase shunt fraction, it is rare to find patients with substantial hypoxemia.[60] The related dyspnea is generally not a lung problem due to lung collapse or to a reduction in pulmonary-function measures.[61] Rather, the dyspnea is a chest-wall issue caused by the diaphragm being displaced caudally, which is mechanically disadvantageous for its length–tension relationship.[61,62] The genesis of the dyspnea is important, since the most clinically relevant questions after large-volume

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thoracentesis are "Is the patient's breathing better?" and "Did the lung fully reexpand?" If the patient does not feel better after a therapeutic thoracentesis, something else is causing the dyspnea (e.g., pulmonary embolism or lymphangitic carcinomatosis). In such instances, further diagnostic testing should be performed; however, procedures that address the pleural space should not be performed. If the patient's dyspnea has been alleviated with thoracentesis, the effusion was at least a major contributor to the dyspnea, and the dyspnea can be diminished regardless of whether the lung has reexpanded. If the lung has reexpanded, the patient can be considered for pleurodesis, placement of a tunneled pleural catheter, or combination approaches, whereas if the lung is nonexpandable, a tunneled pleural catheter is the treatment of choice (Fig. 3).[1,63]

Tunneled pleural catheters are small-bore tubes that are tunneled subcutaneously into the pleural space, can be placed in the outpatient setting, and allow patients or caregivers to drain pleural fluid without subjecting the patient to additional invasive procedures. Because at least 30% of patients with malignant pleural effusion do not have reexpansion of the lung, which may not be evident even at the time of thoracoscopy,[64,65] it may be important to perform a large-volume thoracentesis before deciding on definitive therapy for such patients. The goals of treating patients with malignant pleural effusion are to improve quality of life, primarily by minimizing dyspnea, and to minimize pleural procedures and the need for repeated hospital or doctor visits. Given the poor prognosis of these patients, early and definitive pleural palliation — as opposed to multiple thoracenteses, which expose the patient to both risk and inconvenience — is recommended.[66]

The LENT score (LDH in pleural fluid, Eastern Cooperative Oncology Group [ECOG] performance status, neutrophil–lymphocyte ratio in the serum, and tumor type) has been shown to accurately stratify patients into high-, moderate-, and low-risk groups and may be helpful in guiding therapy.[59] A score of 0 is assigned for a pleural fluid LDH level lower than 1500 IU per liter and a score of 1 is assigned for a level above that threshold, scores of 0 to 3 for worsening ECOG status, a score of 0 for a serum neutrophil–lymphocyte ratio of less than 9 and a score of 1 for a ratio above that threshold, and scores of 0 to 3 based on tumor type. Total scores of 0 or 1 are considered to indicate low risk and are associated with a median survival of 319 days, as compared with a median survival of 130 days in the medium-risk category (scores of 2 through 4) and 44 days in the high-risk category (scores of 5 through 7).[59] For patients in the high-risk category, less invasive approaches, such as placement of a tunneled pleural catheter or even thoracentesis, may be most useful, whereas patients who are considered at low risk can be treated with tunneled pleural catheters, pleurodesis, or combination approaches. When discussing options for patients who have expandable lungs, the risks and benefits of each procedure should be reviewed. The benefits of tunneled pleural catheters include clinically significant improvement in dyspnea, placement in the outpatient setting, and the ability of many patients and families to care for the catheter themselves at home. However, patients need to drain such a catheter repeatedly until the effusion resolves or until death. Spontaneous pleurodesis is estimated to occur in approximately 50% of patients; among patients in whom it does occur, it occurs at a mean of approximately 60 days after insertion of the catheter.[67,68]

The benefits of pleurodesis include substantial alleviation of dyspnea and not having to manage a catheter. However, many centers will keep patients in the hospital for 3 to 5 days after the instillation of talc to effect pleural surface fusion, and there is a small risk of transient hypoxemia associated with the use of nongraded talc.[64,69]

An unblinded randomized trial examined tunneled pleural catheters versus talc-slurry pleurodesis for the treatment of persistent effusions and showed no significant differences in dyspnea or in quality of life.[70] Patients in the talc group underwent more additional procedures, whereas the patients in the tunneled pleural catheter group had a higher incidence of nonserious adverse events. Although it is often a fear of referring health care providers, infection related to the tunneled pleural catheter occurs approximately 5% of the time and can usually be treated without removing the catheter.[71] Trials have suggested that the combination of tunneled pleural catheters with sclerosing agents (talc or silver nitrate) as well as daily drainage (as opposed to

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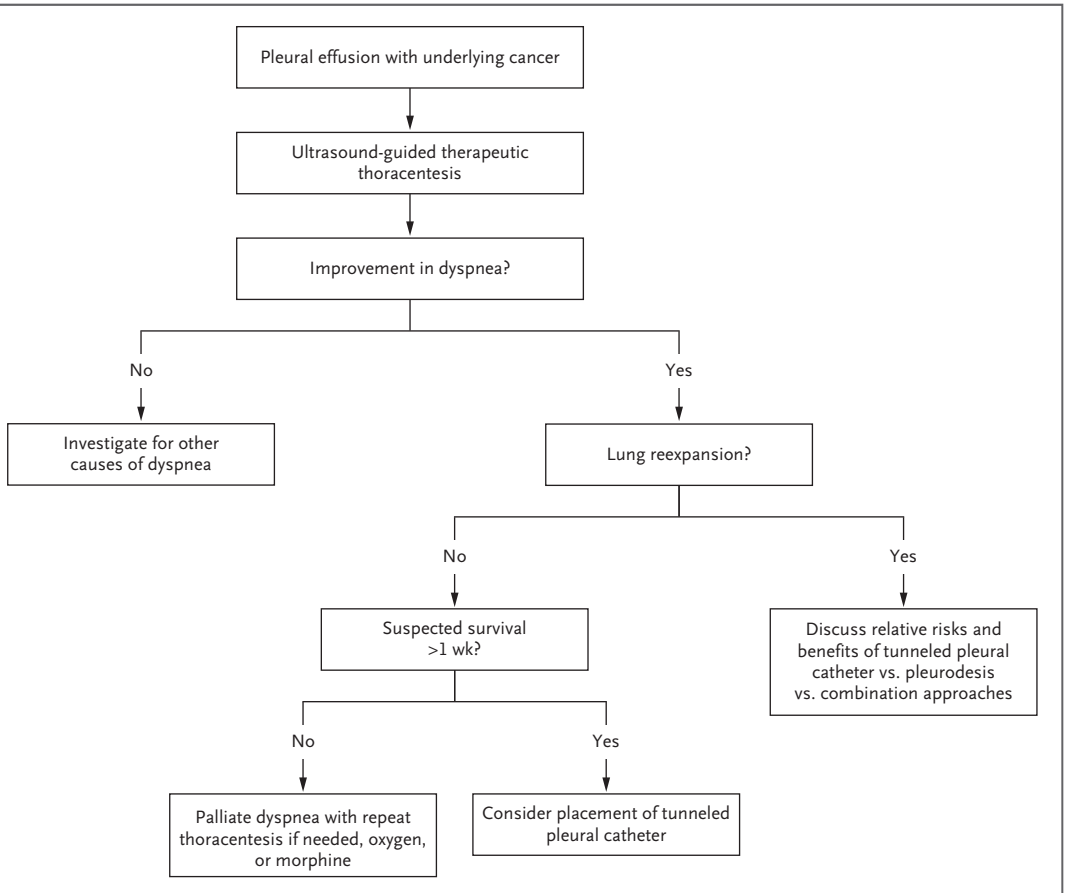

Figure 3. Management of Malignant Pleural Effusions.
The figure is modified from Roberts et al.[63]

drainage every other day) can result in substantially fewer days with a catheter.[72-74] As with all procedures, we recommend that the risks, benefits, and alternatives always be discussed with the patient in detail and that therapy be individualized.

COMPLICATED TRANSUDATES

Congestive heart failure, cirrhosis, and the nephrotic syndrome underlie most transudative effusions.[1] Although often considered benign conditions, effusions associated with congestive heart failure, hepatic failure, and renal failure have recently been shown to be associated with 1-year mortality rates of 50%, 25%, and 46%, respectively.[75] Patients with congestive heart failure and pleural effusion have a 1-year risk of death similar to that of patients who are admitted to the intensive care unit with acute decompensated heart failure, patients with hepatic hydrothorax have a risk of death similar to that of patients with a Model for End-Stage Liver Disease (MELD) score of 20 to 29 (a typical indication for transplantation; MELD scores range from 6 to 40, with higher scores indicating more advanced liver disease), and patients with renal failure and effusion have a 1-year risk of death that is triple that among patients undergoing hemodialysis who do not have effusions.[75] Although in the majority of patients, transudative effusions can be managed by treatment of the underlying condition, refractory effusions deserve prompt and aggressive pleural palliation that will minimize repeat procedures and breathlessness and maximize quality of life. As with malig-

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nant pleural effusions, tunneled pleural catheters, pleurodesis, or both may be indicated for these patients,[76-79] and we recommend careful discussion with relevant teams (e.g., hepatology and liver transplantation) to develop a multidisciplinary plan.

CURRENT CONCEPTS IN THE TREATMENT OF PNEUMOTHORAX

Pneumothorax has traditionally been categorized as primary (no underlying lung disease), secondary (underlying lung disease present), traumatic, and iatrogenic. Because of advances in chest imaging (CT and thoracoscopy), patients with a pneumothorax who had previously been considered free of parenchymal disease have been found to have emphysema-like pulmonary changes and increased pleural porosity, or defects in the visceral pleura that are independent of blebs or bullae.[80] These findings suggest that the distinction between primary and secondary pneumothorax is perhaps an artificial construct and that therapy should be guided by size of the pneumothorax and by the patient's symptoms.[81] Furthermore, there is no standard definition of pneumothorax size; the American College of Chest Physicians defines "large" as a distance of 3 cm or more from the apex of the lung to the cupula of the chest wall,[82] whereas the British Thoracic Society defines it as an intrapleural distance of at least 2 cm at the level of the hilum.[83] In fact, agreement on size based on these definitions occurs less than 50% of the time in clinical settings, which leads to substantial variation in treatment recommendations.[84]

Up to 70% of patients with a clinically stable pneumothorax can be treated with simple needle aspiration, which avoids hospitalization. As with parapneumonic effusion and empyema, guidelines currently recommend the use of small-bore (14-French) chest tubes rather than large-bore chest tubes for patients with pneumothorax who have treatment failure or are not candidates for simple needle aspiration.[83] The latter group includes patients who live far from the treating center, who have minimal social support, or who have more substantial underlying lung disease. Over the past several years, more conservative therapy has been a trend associated with reserving surgical therapy for patients with the highest risk of recurrent pneumothorax. Digital air-leak monitoring devices have been shown to reduce the number of days a chest tube is in place and to shorten the length of stay in the hospital after lobectomy or segmentectomy.[85]

When patients with a pneumothorax are treated with chest tubes, the lung usually expands and the air leak ceases within 3 days. If the lung does not expand fully within 3 to 5 days, consideration should be given to thoracoscopy. At thoracoscopy, blebs are stapled and an effort is made to create a pleurodesis, usually with pleural abrasion. Another method of treating prolonged air leak is to instill 1 ml of the patient's own blood per kilogram of body weight through the chest tube.[86] Alternatively, pleurodesis can be attempted through instillation of a sclerosing agent or the placement of endobronchial one-way valves, with the goal of reducing air flow across the visceral pleura. The valves are then removed after the pleural defect has healed, typically in 6 weeks.[87]

After a patient has had a spontaneous pneumothorax, the likelihood of a recurrence exceeds 50%.[88] Prevention of recurrence is key, especially in patients with markedly decreased lung function, for whom a recurrence can be fatal. If a patient has a first recurrence, then the likelihood of a second recurrence is very high. Recurrence rates can be reduced to approximately 25% if an agent such as talc or doxycycline is instilled through a chest tube and can be reduced to less than 5% with thoracoscopy and the insufflation of talc, stapling of blebs, or pleural abrasion to create a pleurodesis.[89] However, a bullectomy alone, without attempts at pleurodesis, is associated with a higher recurrence rate, and therefore pleurodesis should always be considered an integral part of the procedure.[81]

AREAS FOR FUTURE RESEARCH

Over the past few years, large, multicenter, randomized trials have been published from centers that have large clinical and research pleural services. These trials may lead to improvements in diagnostic tests to establish the underlying cause of a pleural effusion, more compounds to decrease the rate of pleural fluid production or increase the rate of pleural fluid reabsorption, an improved compound for pleurodesis, and fur-

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ther development of interventional pulmonology services and dedicated multidisciplinary pleural disease services. Furthermore, trials investigating the clinical effect of pleural manometry, studies to better understand the pharmacodynamics of drugs in the pleural space, and investigation of how pleural disease is related to the genetic makeup of affected patients may be forthcoming. Patient-centered (and caregiver-centered) outcomes, such as the effect on daily quality of life, are also being investigated. Pleural disease remains a common clinical problem, and expeditious, multidisciplinary evaluation and treatment will maximize the care of our patients.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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